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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,495	04/13/2006	Gabriella Sozzi	0471-0291PUS1	7078

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EXAMINER

TUNG, JOYCE

ART UNIT	PAPER NUMBER
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1637

NOTIFICATION DATE	DELIVERY MODE
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04/02/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/538,495	Applicant(s) SOZZI, GABRIELLA	
	Examiner Joyce Tung	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 9/2/08.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4 and 6-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,4 and 6-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/02/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The response filed 9/2/08 to the Office action has been entered. Claims 1, 3-4 and 6-11 are pending.

1. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph is withdrawn because of the amendment filed 9/2/08.

2. Regarding the rejections as set forth in sections 5-7 of the Office action mailed 5/30/08, the response argues that the present invention is a methodology of quantification of plasma circulating DNA through the amplification of hTERT copy number as a marker and the teaching of the prior art documents is that plasma or serum hTERT RNA is indicative of tumor gene expression levels and therefore may be used as a tumor marker. However, Chang et al. disclose the quantitation of expression of hTERT mRNA (See column 2, lines 1-3) and that quantitation of a sample containing an unknown number of target sequences typically is carried out with reference to a "standard curve" generated from a series of amplifications of samples containing the target sequence in a range of known amounts (See column 10, lines 14-18). The instant claim 1 recited "determining the DNA concentration in the DNA preparation by interpolation of a calibration curve calculated with known amounts of DNA". The recitation as amended is not clear that the concentration of circulating total DNA in a plasma sample is determined by quantification of hTERT copy number. Therefore, the teachings of the references cited in the rejections satisfy the limitations of the claims. Thus the rejections are maintained and reiterated as follows.

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3. Claims 1, 3-4, 7-8 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (6,664,046, issued Dec. 16, 2003) in view of Cook (7,160,996, issued Jan. 9, 2007) and Sozzi et al. (Cancer Research, June 15, 2001, Vol. 61, pg. 4675-4678).

Chang et al. disclose a method of quantitation of expression of hTERT mRNA (See column 2, lines 1-3). The level of hTERT mRNA expression assists in the diagnosis of cancers (See column 2, lines 9-10). The method involves amplifying a target hTERT mRNA sequence using a pair of primers (See column 2, lines 46-47). The amplification is carried out using a DNA polymerase with 5' to 3' exonuclease activity. The amplified hTERT mRNA sequence is detected by probe hybridization (See column 2, lines 59-62). The detection probe is labeled with two fluorescent dyes, one of which is capable of quenching the fluorescence of the other dye. One dye is attached to the 5' end and the other is attached to an internal site (See column 9, lines 47-55, and column 19, lines 9-15). Quantitation of a sample containing an unknown number of target sequences typically is carried out with reference to a "standard curve" generated from a series of amplifications of samples containing the target sequence in a range of known amounts (See column 10, lines 14-18).

Chang et al. do not disclose one quencher or one reporter fluorophore located at the 3' end.

Cook discloses a new class of fluorescence energy transfer probes with optimized characteristics for genetic detection, discrimination and quantitation (See column 3, lines 43-45) in which a quencher is located at the 3' end of the probe (See fig. 5).

One of ordinary skill in the art would have been motivated to apply the probe of Cook in the method of Chang et al. for the quantitation of expression of hTERT mRNA because the

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probes of Cook possess optimized characteristics for genetic detection, discrimination and quantitation (See column 3, lines 43-45). It would have been prima facie obvious to use a probe which has a quencher located at the 3' end of the probe.

Chang et al. do not explicitly disclose the reference concentration as recited in claim 4.

However, one of ordinary skill in the art would have been motivated to optimize the reference concentration with a reasonable expectation of success because optimization of reaction conditions was a routine practice in the art at the time the invention was made. It would have been prima facie obvious to apply a reference concentration as recited in claim 4.

None of the references above discloses determining the concentration of circulating DNA in a plasma sample from a cancer patient.

Sozzi et al. disclose that in lung cancer patients, the mean values of plasma DNA concentration were higher than in controls even considering stage Ia patients. The data suggest that quantification of plasma DNA in lung cancer patients are valuable noninvasive diagnostic tools for discriminating from unaffected individuals and for detecting early recurrence during follow-up (See pg. 4675, the Abstract).

One of ordinary skill in the art would have been motivated to determine the concentration of circulating DNA in a plasma sample from a cancer patient because of the advantages as disclosed by Sozzi et al. as discussed above. It would have been prima facie obvious to determine the concentration of circulating DNA in a plasma sample from a cancer patient.

4. Claim 6 rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (6,664,046, issued Dec. 16, 2003) in view of Cook (7,160,996, issued Jan. 9, 2007) and Sozzi et al. (Cancer Research, June 15, 2001, Vol. 61, pg. 4675-4678) as applied to claims 1, 3-4, 7-8 and

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10-11 above, and further in view of Wick et al. (Gene, 1999, Vol. 232, pg. 97-106), Buck et al. (BioTechques, 1999, Vol. 27(3), pg. 528-536) and the attached search report.

The teachings of Chang et al., Cook and Sozzi et al. are set forth in section 3 above. None of the references discloses SEQ ID NO: 1-3 used as primers and a probe for amplifying the fragment of hTERT gene.

Wick et al. disclose the complete genomic organization of the hTERT gene and isolated the 5'- and 3' flanking region. The hTERT gene encompasses more than 37kb and consists of 16 exons. These results provide the basis for more detailed studies on the regulation of telomerase activity in normal and cancer cells and may lead to the development of new cancer therapies (See pg. 97, the Abstract). As indicated in the search report, the nucleic acid sequence of the hTERT gene comprises SEQ ID NO: 1-3 (See the attached search report).

Buck et al. disclose strategies of sequencing primer selection and evaluated primer performance in automated DNA sequencing (See pg. 528, the Abstract). The results were surprising in that nearly all of the primers yielded data of extremely high quality (See pg. 535, column 2, second paragraph).

One of the ordinary skill in the art would have been motivated to design primers and probes from a well known nucleic acid sequence, for example, the nucleic acid of hTERT gene as disclosed by Wick et al. for amplifying the fragment of the hTERT because Buck et al. disclose strategies of sequencing primer selection and all of the primers yielded data of extremely high quality (See pg. 535, column 2, second paragraph). It would have been prima facie obvious to apply SEQ ID NO: 1-3 as primers and probes for amplifying a fragment of hTERT gene.

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5. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (6,664,046, issued Dec. 16, 2003) in view of Cook (7,160,996, issued Jan. 9, 2007) and Sozzi et al. (Cancer Research, June 15, 2001, Vol. 61, pg. 4675-4678) as applied to claims 1, 3-4, 7-8 and 10-11 above, and further in view of Gocke et al. (6,156,504 issued Dec. 5, 2000).

The teachings of Chang et al., Cook and Sozzi et al. are set forth in section 5 above. None of the references disclose the limitation of claim 9.

Gocke et al. disclose the methods for detecting the presence of extracellular DNA in blood plasma via DNA amplification for the detection, monitoring or evaluation of cancer or premalignant conditions (See column 3, lines 66-67 and column 4, lines 1-7). The invention provides a method of screening both healthy individuals, and individuals at risk for cancer and premalignant conditions (See column 8, lines 59-61) in which lung cancer from smokers is detected (See column 30, lines 63-67).

One of ordinary skill in the art would have been motivated to apply the method of Chang et al. for the evaluation of the risk of cancer development in smokers because the method of Gocke et al. discloses detecting the presence of extracellular DNA in blood plasma via DNA amplification for the detection, monitoring or evaluation of cancer or premalignant conditions (See column 3, lines 66-67 and column 4, lines 1-7). It would have been prima facie obvious to carry out evaluation of the risk of cancer development in smokers.

Summary

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joyce Tung whose telephone number is (571) 272-0790. The examiner can normally be reached on Monday - Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

/Joyce Tung/
Examiner, Art Unit 1637
March 3, 2009